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FOOD EFFECT RISK ASSESSMENT IN PREFORMULATION STAGE USING MATERIAL SPARING µFLUX METHODOLOGY

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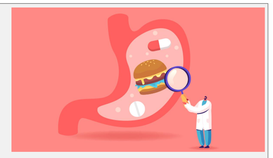
PURPOSE



- The intake of food and meal type can strongly impact the bioavailability of orally administered drugs and can consequently impact drug efficacy and safety.
- Assessing food effect (FE) on drug absorption is critical to optimize the safety and efficacy of the final product.
- During the early stages of drug development, when only a small amount of drug substance is available, scientists might not be aware of the mechanism of food effect, and the limiting steps in oral absorption of a new drug candidate.
- **The aim of this study** was to investigate the suitability of a small volume dissolution-permeation set up to predict food effect early in preformulation stage using drug substance alone.

METHOD(S)

µFLUX dissolution-permeation set up

- Dissolution/permeation measurements were performed using µFlux apparatus (Pion Inc.) with 4 side-by-side donor-receiver chambers.
- FaSSIF (Fa) or FeSSIF (Fe) media were used in the donor compartments and Acceptor Sink Buffer (ASB pH 7.4) in the acceptors, separated by a lipophilic membrane (PVDF filter support 1.54 cm^2 covered with GIT Lipid).
- Unformulated drugs were added as a powder into the donors and concentration was monitored in both chambers using *in-situ* fiber optic probes with UV-Vis spectrometer (Rainbow R2D8, Pion Inc).
- Direct or second derivative spectral analysis and path length from 2-20 mm were used to further improve concentration analysis.
- 11 model compounds (BCS class I-IV) with diverse physicochemical properties and published human clinical data on food effects were selected.

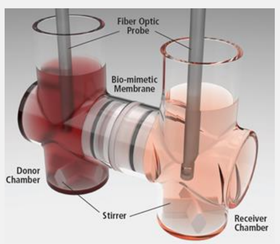


Figure 1*: Schematic of uFLUX pairs used in the study*

The flux (J) across the membrane was calculated from the concentration-time profiles in the receiver compartments

$$J(t) = \frac{dm}{A.dt} = \frac{V}{A} \cdot \frac{dc}{dt}$$

RESULT(S)

- 11 model compounds (BCS class I-IV) with diverse physicochemical properties and published human clinical data on food effects were selected.
- Solubility ratio (fed/fasted) was calculated using biorelevant solubility data obtained from the literature.
- PK parameters, total drug exposure AUC, the maximum concentration C_{max} in the fasted and fed state were obtained from the published clinical data.
- Food effect was assigned based on AUC and C_{max} ratios as follows: **positive food effect** (AUC and/or C_{max} increase with food, 4 compounds), **negative food effect** (decrease in AUC and/or C_{max} with food, 4 compounds) and **no food effect** (no significant difference with food, 3 compounds).
- C(t) in acceptor chambers of µFLUX pairs were used to calculate flux values corresponding to the dissolution in the donor chambers with FaSSIF or FeSSIF.

Table 1: Physicochemical properties, Food effect data and measured Flux of the studied compounds

Drugs	BCS Class	Log P	Solubility Ratio	Observed AUC Ratio	Observed C_{max} Ratio	FE (clinical)	Dose clinical data	Dose flux study	Flux Fe (±SD; n=3)	Flux Fa (±SD; n=3)	Flux Ratio	FE (predicted)
			(Fed/Fasted)	(Fed/Fasted)	(Fed/Fasted)		(mg)	(mg)			(Fed/Fasted)	
Amiodarone (early)	II	7.8	2.23	2.36	3.68	positive	600	200	0.073 ± 0.001	0.017± 0.003	4.25	👍
Amiodarone (late)	II	7.8	2.23	2.36	3.68	positive	600	200	1.277± 0.109	0.579 ± 0.095	2.21	👍
Celecoxib	II	3.02	2.24	1.19	1.29	positive	200	50	0.632 ± 0.077	0.186 ± 0.021	3.4	👍
Clopidogrel bisulfate	II/IV	4.2	3.85	1.02	0.79	none	75	75	2.168 ± 0.323	1.751 ± 0.540	1.24	👍
Danazol	II	4.7	3.43	3.13	2.73	positive	100	100	0.352 ± 0.063	0.081 ± 0.016	4.35	👍
Fluoxetine HCl	I	4.5	1.17	0.96	0.85	none	40	40	0.85 ± 0.01	1.77 ± 0.15	0.5	X
Furosemide	IV	2.56	0.23	1.18	0.67	negative	40	80	0.208 ± 0.036	0.018 ± 0.003	11.48	X
Griseofulvin	II	2.2	1.24	1.7	2.2	positive	1000	125	0.218 ± 0.009	0.205 ± 0.011	1.06	👍
Isoniazid	I	-0.52	n/a	0.88	0.49	negative	300	300	0.020 ± 0	0.020 ± 0	1.02/0.92	X
Nefazodone HCl	II	3.5	1.52	0.78	0.93	negative	200	50	1.077 ± 0.084	0.521 ± 0.179	2.07	
Nefazodone HCl susp.	II	3.5	1.52	0.78	0.93	negative	200	100	1.923 ± 0.547	2.610 ± 0.618	0.74	👍
Nifedipine	II	3.17	3.2	1.02	0.74	none	10	25	0.235 ± 0.028	0.233 ± 0.073	1.01	👍
Zidovudine	III	0.13	n/a	0.9	0.3	negative	100	200	0.034 ± 0.002	0.037 ± 0.007	0.92	👍

Dissolution and appearance kinetic profiles

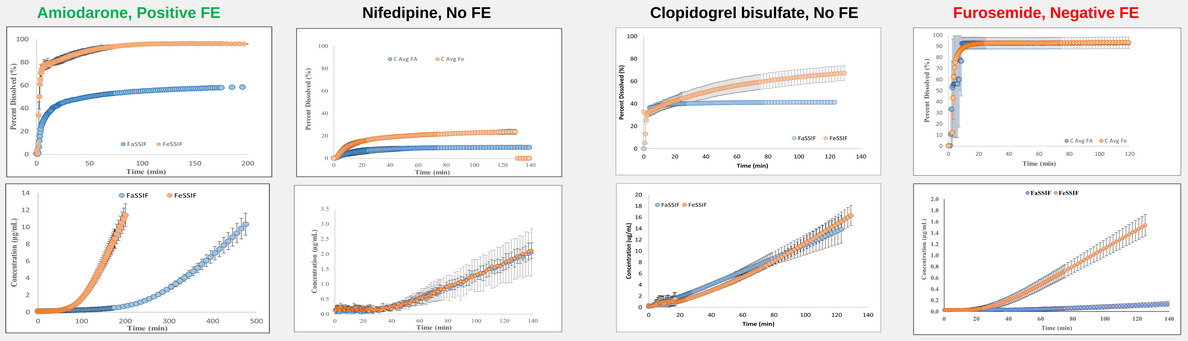


Figure 2*: Concentration-time profiles from donors (top) and receivers (bottom) for Amiodarone, nifedipine, clopidogrel bisulfate and furosemide.*

- **Positive FE:** BCS II drugs that showed positive FE in the clinic also showed flux(fed/fasted) ratio >1 indicating positive FE.
- **No FE:** clopidogrel bisulfate & nifedipine, solubility ratio indicates a positive FE while clinical data reported no FE. Flux ratio was more predictive of FE.
- **No FE:** fluoxetine HCL is reported to have no FE. Solubility ratio also shows no FE. However, flux ratio indicates a negative FE. Flux experiments conducted in the absence of lecithin and taurocholate also shows no FE. For this BCS I drug, FE prediction based on µFLUX was not reliable.
- **Negative FE:** furosemide is more ionised at pH 6.5 (Fa) compared to pH 5 (Fe), thus solubility is greater in Fa compare to Fe which correlates with a negative FE found in the clinic. Since only uncharged species can permeate through the lipophilic membrane it is expected that membrane permeability is higher at pH 5 compare to 6.5 and because of the pH difference, flux was not predictive of FE.

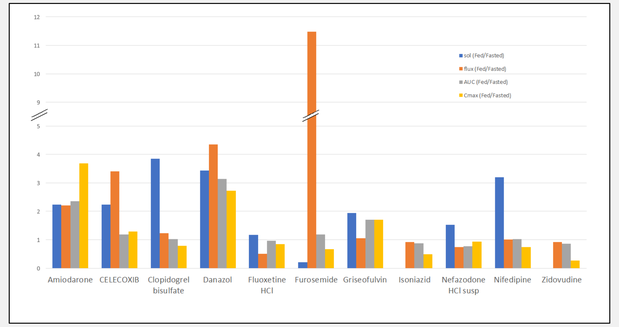


Figure 3*: Solubility, flux, AUC and Cmax ratios for the studied compounds.*

- Side by side comparison of solubility, flux, and AUC with C_{max} ratios shows that flux ratio is more predictive than solubility ratio for FE prediction

CONCLUSION(S)

- Using 11 model compounds with diverse physicochemical and pharmacokinetic properties, we showed that a combination of dissolution-permeation is a useful and more predictive tool than the solubility ratio alone to predict food effect
- As no *in vitro* technique can predict intestinal drug metabolism or the impact of transporters on drug absorption, the flux-based method could not predict the negative food effect successfully but may provide very good qualitative insight about the food effect of permeability limited, dissolution rate limited and solubility limited compounds
- This study shows that during early stages of drug development, scientists can use the µflux dissolution-permeation set up with a limited amount of unformulated drug substance to gain valuable insight on the limiting steps in oral drug absorption and the mechanism of FE of new drug candidates

REFERENCE

(1) C. Jankovsky, O. Tsinman, N. K.Thakral,, Food effect risk assessment in preformulation stage using material sparing uFLUX methodology, *ADMET&DMPK* (under review)

(2) A. Avdeef, *Absorption and Drug Development*, John Wiley & Sons, Inc., Hoboken, New Jersey, USA, 2012, p. 342. ISBN 978-1-118-05745-2

(3) T. Zhang, E. Wells. A review of current methods for food effect prediction during drug development, *Current Pharmacology Reports*. **6** (2020) 267–279

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Pion

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